

REMARKS

By the present communication, claim 26 is amended and claims 1, 5, 6, and 27 are cancelled. Upon entry of the present amendment, claims 7, 11-13, 26, and 28 will be pending and under examination in the application. No new matter has been added as support for the amended claim language is found throughout the application as filed. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Rejections Under 35 U.S.C. § 102 (b)

In the Office Action, claims 1 and 5 stand rejected under 35 U.S.C. § 102(b), as being allegedly anticipated by Jagdev *et. al.* (*British Journal of Cancer*, 2001, 84:1126-1134). This rejection is rendered moot by cancellation of claims 1 and 5.

II. Rejections Under 35 U.S.C. § 103 (a)

In the Office Action, claims 7, 11, 26, and 28 stand rejected under 35 U.S.C. § 103(a), as being allegedly unpatentable over Jagdev *et. al.* (*British Journal of Cancer*, 2001, 84:1126-1134). The Office asserts that the prior art reference teaches treatment of breast cancer with a combination of Paclitaxel and Zoledronic acid, which results in synergistic effects on breast cancer cell number and apoptosis. Applicants respectfully traverse this rejection in view of the surprising and unexpected results of the claimed sequence of administration.

The instant invention as defined by claim 28 recites a method of sequential administration of paclitaxel (or other chemotherapeutics) and zoledronic acid or its salt. As emphasized in the published application (US 2007/0219115) on page 2, ¶ [0015], “the sequential use of a chemotherapeutic agent such as paclitaxel or letrozole and a bisphosphonate advantageously gives rise to enhanced, or even synergistic, levels of cancer cell growth inhibition or cancer cell apoptosis.” Indeed, “[t]he order in which the agents are given significantly affects the maximum level of apoptosis achieved.” *Id.*, p. 1, ¶ [0004].

A comparison of experimental data in the cited art and present invention clearly indicates that a surprising and unexpected multifold enhancement in activity is observed with a specific sequence of administration of the individual agents. For instance, Jagdev *et. al.*, in an example

on page 1130, discloses that administration of zoledronic acid and paclitaxel together caused a two-fold increase ($p < 0.02$) in the proportion of apoptotic MCF-7 cells when compared with either drug alone, as determined by nuclear morphology analysis. By contrast, the present application shows that when zoledronic acid is administered after paclitaxel, a ten-fold increase ($p < 0.001$) in induction of apoptosis occurs (Experiment 1 Results, page 5, ¶ [0080]). The present application further demonstrates that a forty-fold increase ($p < 0.004$) in induction of apoptosis occurs when zoledronic acid is administered after paclitaxel in a clinically relevant dosing amount of 1 μ M (Experiment 2 Results, page 5, ¶ [0082]). Moreover, these pronounced effects are achieved with shorter incubation periods for both paclitaxel and zoledronic acid. The cited art teaches incubation periods in the range of 72 hours [page 1127, under the title 'Measurement of cell number'] as compared to the 4 hours for paclitaxel and 1 hour for zoledronic acid disclosed in the present application [page 5, Experiment 1-3]. There is simply no expectation that such dramatic improvements in therapeutic efficacy could be achieved by the present method.

Further, with respect to claim 26, Applicants respectfully submit that the surprising and unexpected result obtained when the claimed combination of drugs is used as recited in the instructions, renders claim 26 non-obvious as well.

Because the differences between the claimed methods and the prior art lead to surprising and unexpectedly superior anticancer activity, Applicants respectfully submit that the present claims are nonobvious, and request withdrawal of this rejection.

CONCLUSION

In view of the above remarks, reconsideration and favorable action on all claims are respectfully requested. Should any issues remain to be addressed in view of the present response, the Examiner is respectfully requested to contact the undersigned at the telephone number provided so that a prompt disposition of the application may be achieved.

Respectfully submitted,

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